UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/772,913	02/05/2004	Steven W. Dow	86715.0002	5237

20350 7590 06/06/2007

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
06/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/772,913	DOW ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-20,24-31,50-53 and 56-67* is/are pending in the application.

4a) Of the above claim(s) *8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,9-20, 24-31, 50-53 and 56-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 3/2/07 has been entered. As noted in the Notice of non-responsive amendment mailed on 2/12/07, applicant's initial response to the restriction requirement received on 11/14/06 elected Invention II. However, applicant's supplemental response received on 11/20/06 stated that the supplemental response was intended to supercede the previous response, see page 1 of the response. This supplemental response elected Invention IV, and further elected interferons as the species of cytokine. The instant response further elects lung cancer as the source of tumor antigens. It is noted that as the applicant did not indicate that the election of Group IV was made with traverse or provide any arguments traversing the restriction requirement, the election of Group IV is considered to have been made without traverse and is made FINAL. It is further noted, however, that the applicant's election of species of interferon and lung cancer were made with traverse. A response to the traversals is presented below.

The applicant argues that the election of species requirements are misplaced as all the independent claims in original Group IV, i.e. claims 50-53, do not recite the limitation regarding a recombinant nucleic acid encoding a cytokine. The applicant further cites *In re Weber* and *In re Haas* and MPEP 803.02 in support of their argument. The applicant also argues that if prior art is not found on the elected species, that the search should be extended to the next species. In response, *In re Weber*, *In re Haas*, and MPEP 803.02 deal with Markush type claims. Claim 52 is not a Markush claim, but rather a simple generic claim. It is further noted that although claims 50-51 and 53 clearly encompass the additional element of a nucleic acid encoding a cytokine,

there was no statement or indication that examination of those claims would somehow be limited to particular limitations of claim 52. The purpose of the election of species requirement was to ease the burden on the examiner in searching and examining the claims as they read on the further inclusion of a recombinant nucleic acid encoding a cytokine in the instant methods and compositions. Regarding extending the search to additional species should the elected species be found free of the prior art, note that the in election of species requirements addition species are only entitled to consideration upon the allowance of a generic claim, see MPEP 809.02 and 37 CFR. 1.141. Allowance of a generic claim requires more that just consideration of patentability under 35 U.S.C. 102 and 103, it further requires consideration of additional statutes including 35 U.S.C. 112, first and second paragraphs. Finally, the previous office action set forth the specific reasons why search and examination of the various species of cytokines or tumor cells claimed would place an undue burden on the examiner. Thus, applicant's traversal is not found persuasive and the election of species requirements are made FINAL. However, please note that upon further consideration, the examiner has decided to withdraw the election of species requirement based on the tumor cell source of the tumor antigens. The election of species requirement regarding cytokines is maintained.

Following applicant's claim amendment filed on 11/20/06, claims 1-6, 21-23, 32-49, and 54-55 have been canceled, and new claims 66-67 have been added. Claims 7-20, 24-31, 50-53 and 56-67 are currently pending in the instant application. Of these, claim 8 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election)

requirement in the reply filed on 11/20/06. Claims 7, 9-20, 24-31, 50-53, and 56-67 are therefore currently under examination in the instant application. An action on the merits follows.

Priority

The office acknowledges applicant's claim for benefit of priority to parent application 09/104,759 which is set forth in the first paragraph on page 1 of the specification. However, the status of the parent application has not been provided. It is noted that this application has issued as a U.S. Patent. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 9-20, 24-31, 50-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of reducing the number of lung metastases of a colon carcinoma by intravenous administration of cationic DOTAP:cholesterol liposomes comprising total autologous tumor RNA alone or total autologous tumor RNA and DNA encoding interferon-gamma operatively linked to a constitutive promoter, does not reasonably provide enablement for methods of reducing the size of any tumor, elimination of any tumor, or prevention of the formation of any tumor or metastatic cancer using the instant methods as claimed. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification is largely drawn to the generation of non-specific immune responses using various DNA molecules in the form of oligos or empty plasmids. The specification does however disclose methods of generating tumor specific immune responses comprising administering total RNA derived from a tumor and cationic liposome with or without DNA encoding a cytokine such as interferon-gamma. The specification also provides a working example of the invention where total RNA derived from CT26 colon carcinoma cells and cationic liposomes are intravenously injected into a mouse in which experimental lung metastases had been induced by intravenous injection of CT26 colon carcinoma cells. The example demonstrates that the autologous total RNA complexed to DOTAP:cholesterol liposomes was able to reduce the number of lung nodules but not prevent the formation of lung nodules as compared to controls. The example also demonstrates that tumor specific CTL were generated. However, the data provided does not demonstrate that the CTL response or any other immune response generated was capable of completely eradicating either an established primary tumor located anywhere in the mouse, or any metastases located anywhere in the mouse, or of completely preventing the formation of any solid or liquid tumor or tumor metastases stemming from such tumors. The model system used corresponds to a local delivery system since the specification teaches that cationic liposome/nucleic acid complexes when injected intravenously localize to the lungs. Thus, while the example shows that local administration of the RNA/liposome complexes can stimulate immune cells in the vicinity of the lung metastases, the

working example does not demonstrate that the immune response generated would be effective in reducing or preventing the growth of distal primary tumors or metastases.

It is noted that in order for a CTL to kill a target cancer cell, the tumor cell would need to present the same peptide/MHC complex as the stimulating antigen presenting cell. At the time of filing, Restifo et al. teaches that tumors evade immune responses by a variety of mechanisms including down-regulation or mutation of antigen processing molecules such as TAP and MHC-encoded proteasome components, loss of antigenic epitopes by either lack of expression or mutations, loss of functional β_2m expression , and loss of MHC class I alleles (Restifo et al (1993) J. Immunother., Vol. 14, pages 182-190). The loss or mutation of any of these molecules would prevent the expression of tumor specific peptide/MHC class I complex on the cell surface and thus prevent the recognition of the tumor by any activated T cells. It is further noted in regards to the use total RNA derived from multiple allogeneic tumors of the same histological type as the tumor to be treated that the expression of proteins, and tumor antigens in particular, in tumor cells of the same histologic type can be extremely heterogenic. For example, Chen et al. demonstrates that expression of gp100 varies substantially in different melanoma tumors, with some melanomas not expressing gp100 at all (Chen et al. (1995) Proc. Natl. Acad. Sci., Vol. 18(2), 8125-8129). Thus, the state of the art at the time of filing sets forth the obstacles in utilizing CTL specific for tumor antigens to kill tumor cells. Thus, in view of the art recognized problems in targeting patient derived tumors for killing by CTL, including antigen presentation deficiencies and heterogeneity in the expression of tumor antigens, the limitation of the *in vivo* working examples to a reduction in the number of lung metastases, and the breadth of the claims, it would have required undue experimentation to completely eliminate or prevent the growth of

any type of tumor cell by intravenous or intraperitoneal administration of cationic liposomes and total tumor RNA from either an autologous or allogeneic source.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-10 and 66-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites the method of claim 50, "wherein said cytokine is selected from the group consisting of hematopoietic growth factors, interleukins, interferons, immunoglobulin superfamily molecules, tumor necrosis factor family molecules and chemokines". The term "cytokine" is art recognized to define a specific set of soluble proteins which include the interleukin family, the interferons, the TNF family and the lymphoid/myeloid colony stimulating factors (G-CSF, GM-CSF). Claim 26 recites an improper markush group which includes proteins which are not art-recognized as cytokines. Chemokines, for example are a separate family of proteins with substantially different physiological activities than most cytokines. Chemokines such as RANTES, the MIPs, MCPs, etc. are not considered "cytokines" by the skilled artisan. Likewise, the genus of hematopoietic growth factors and the genus of immunoglobulin superfamily molecules includes a large number of proteins including antibodies, receptors and cell surface molecules which are also not recognized as cytokines. While the applicants can be their own lexicographers to a certain degree, the use of the term "cytokine" in the claims contrary to its art accepted definition renders the claim confusing and indefinite as to the metes and

bounds of the term "cytokines". Claims 8-10 depend on claim 7 and thus are included in this rejection.

Claims 66-67 depend on claim 50 which recites a method comprising the administration of a therapeutic composition comprising a liposome and total RNA derived from a tumor cell. Claims 66-67 seek to further limit claim 50. However, the limitations in claims 66-67 appear to conflict with the limitations of claim 50. As indicated, claim 50 is drawn to the administration of total RNA. Claims 66-67 appear to indicate that the RNA is "in the form of a plurality of cDNA sequences amplified from said total RNA, each of said cDNA sequences being operatively linked to a transcription control sequence". cDNA, however, is DNA, not RNA. RNA cannot be "in the form of" cDNA. Either it is RNA or it is cDNA, as each is comprised of different molecules, i.e. ribonucleic versus deoxyribonucleic acids. Further, RNA and cDNA have different properties and functions. As such, the claims as written contain conflicting limitations that render the claims confusing in that it is unclear whether the applicant intends to use RNA or cDNA in the methods as claimed. Thus, the metes and bounds of the claims cannot be determined. It is further noted that the elected invention is drawn to liposomes and total RNA. If applicant intends to claim methods and/or compositions comprising liposomes and cDNA, such claims would be subject to restriction and, based on the instant examination of the elected invention of liposomes and RNA, would be withdrawn from prosecution.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 56, 60, 63 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,670,186 (2003), hereafter referred to as Nair et al. Claims 56, 60, and 63 are product claims which recite an intended use of the claimed compositions. However, the MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." *In re Casey*, 152 USPQ 235 (CCPA 1967); *In re Otto* , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02).

Nair et al. teaches RNA/cationic liposome compositions useful for transfecting cells in order to stimulate immune responses where the RNA is total RNA or polyA+RNA derived from a tumor, i.e. mRNA (Nair et al., columns 1-5, especially column 5). Nair et al. further teaches

that the cationic lipids are DOTMA:DOPE (Nair et al., column 9). Thus, by teaching a composition with the same structure as that claimed, Nair et al. anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7, 9-20, 24, 26, 28-30, 50-53, 56-61, and 63-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,589,466 (1996), hereafter referred to as Felgner et al., in view of U.S. Patent No. 6,670,186 (2003), hereafter referred to as Nair et al. Claims 56-61, and 63-64 are product claims which recite an intended use of the claimed compositions. However, the MPEP states that,".. in apparatus, article, and composition claims,

intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." *In re Casey*, 152 USPQ 235 (CCPA 1967); *In re Otto* , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02). It is further noted that independent method claim 50 and dependent claims 51-53, 7, 12-20, 24, and 28-30 are broadly drawn to methods of eliciting a tumor antigen specific and non specific immune response, which encompasses both non-therapeutic and therapeutic immune responses.

Felgner et al. teaches methods of immunizing a mammal by administering a preparation comprising a cationic liposome containing an mRNA encoding an immunogenic peptide, wherein the expression of the immunogen in the cells of a mammal induces immune responses, including humoral and cellular immune responses, including cytotoxic T lymphocytes (CTL) (Felgner et al., columns 7-9, 20-22, 25-26, and 29-32, especially columns 8-9, bridging paragraph, and examples 7-9). In particular, Felgner et al. teaches that the immunogenic peptide is associated with a tumor and induces CTL capable of killing the tumor (Felgner et al., column 8). Felgner et al. further teaches that the preparation can include a nucleic acid encoding a cytokine, and preferably one of the interferons (Felgner et al., column 8 and columns 22-23, bridging paragraph). Felgner et al. also teaches that cationic liposomes can be unilamellar or multilammelar, formed from cationic lipids such as DOTMA, or DOTAP, and other materials such as cholesterol (Felgner et al., columns 25-26). In addition, Felgner et al. teaches that routes of administration of the peptide include intravenous administration and administration to a body cavity (Felgner et al., column 7, and column 32- example 9 for intravenous administration of mRNA/liposomes). Felgner et al. also teaches the inclusion of nonionic materials such as sugars in the preparations (Felgner et al., columns 23, and 32). Felgner et al. further teaches that the

ratio of mRNA to liposome can vary, and exemplifies one ratio of 1:40 mRNA to cationic liposomes (Felgner et al., column 30).

Felgner et al. differs from the instant invention by teaching the use of a single mRNA immunogen associated with a tumor instead of total tumor RNA or total tumor mRNA. Nair et al. supplements Felgner et al. by teaching RNA/cationic liposome compositions useful for transfecting cells in order to stimulate immune responses where the RNA is total RNA or polyA+RNA derived from a tumor, i.e. mRNA (Nair et al., columns 1-5, especially column 5). Nair et al. provides motivation for using total tumor RNA and especially total tumor mRNA by teaching that the use of RNA enriched tumor preparations circumvents the need to isolate and identify a tumor antigen, has the capacity to elicit immune responses against multiple tumor antigen, thus reducing escape mutants, and extends the immunotherapy methods to tumors in which specific tumor antigens have not been identified (Nair et al., columns 1 and 6). Nair et al. further teaches that the RNA can be derived from tumors such as melanomas, breast cancer, prostate cancer, bladder cancer, pancreatic cancer, colon cancer, and ovarian cancer (Nair et al., column 3). Thus, based on the motivation provided by Nair et al. for using total tumor RNA or total tumor mRNA over isolated RNA encoding a tumor antigen in methods to stimulate anti-tumor immune responses, it would have been *prima facie* obvious to the skilled artisan at the time of filing to utilize total tumor RNA or mRNA derived from tumors such as melanomas or colon carcinomas instead of a single mRNA encoding a tumor antigen in the methods of stimulating immune responses in a mammal taught by Felgner et al. Further, the skilled artisan would have had a reasonable expectation of success in using total tumor RNA or total tumor mRNA and cationic liposomes to generate anti-tumor immune responses in view of the

successful use by Felgner of mRNA/cationic liposomes to induce immune responses when administered intravenously and the successful use by Nair et al. of total tumor RNA/cationic liposomes to transfect cells.

Claim 62 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,589,466 (1996), hereafter referred to as Felgner et al., in view of U.S. Patent No. 6,670,186 (2003), hereafter referred to as Nair et al., as applied to claims 7, 9-20, 24, 26, 28-30, 50-53, 56-61, and 63-64 above, and further in view of U.S. Patent No. 5,830,878 (11/3/98), hereafter referred to as Gorman et al.

The combined teachings of Felgner et al. in view of Nair et al. provides sufficient motivation and reasonable expectation of success in making a composition comprising total tumor RNA and a cationic liposome as discussed in detail above. While Felgner et al. provides substantial guidance for making cationic liposomes using various cationic lipids including DOTAP and DOTMA and cholesterol, Felgner et al. does not specifically teach cationic liposomes comprising DOTIM and cholesterol. Gorman et al. supplements the teachings of Felgner et al. by teachings that the state of the art of cationic liposomes formation with nucleic acids for the purpose of transfecting cells was advanced at the time of filing, and by providing specific guidance for making a number of different cationic liposomes including multilammelar liposomes comprising DOTIM and cholesterol (Gorman et al., columns 5-9). Thus, based on the motivation provided by both Felgner et al. and Gorman et al. that many different compositions of cationic liposomes can be combined with nucleic acids and used to successfully transfect cells and the high degree of skill in the art of cationic liposomes as nucleic acid delivery agents at the

time of filing, it would have been *prima facie* obvious to the skilled artisan to utilize DOTIM:cholesterol cationic liposomes as taught by Gorman et al. in the compositions of total tumor RNA/cationic liposomes taught by Felgner et al. and Nair et al. with a reasonable expectation of success.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633